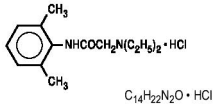
**LIDOCAINE HYDROCHLORIDE - lidocaine hydrochloride injection, solution**
AMERICAN REGENT, INC.

**Rx Only**
FOR INFILTRATION AND NERVE BLOCK
NOT FOR EPIDURAL OR CAUDAL USE

## DESCRIPTION

Lidocaine HCl Injection, USP is a sterile aqueous solution that contains a local anesthetic agent and is administered parenterally. See **INDICATIONS** for specific uses.
Lidocaine HCl Injections, USP contains lidocaine HCl which is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-, monohydrochloride and has the following structural formula:




$C_{14}H_{22}N_2O \cdot HCl$

Lidocaine HCl 1% — Each mL contains Lidocaine HCl 10 mg, Sodium Chloride 7 mg, Methylparaben 1 mg, Water for Injection q.s.
Lidocaine HCl 2% — Each mL contains Lidocaine HCl 20 mg, Sodium Chloride 4.6 mg, Methylparaben 1 mg, Water for Injection q.s.
The pH (range 5.0-7.0) of both strengths is adjusted with Sodium Hydroxide and/or Hydrochloric Acid, when necessary.

## CLINICAL PHARMACOLOGY

MECHANISM OF ACTION: Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic action.
HEMODYNAMICS: Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributed to block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system, and/or the beta-adrenergic receptor stimulating action of epinephrine when present. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.
PHARMACOKINETICS AND METABOLISM: Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.
The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 μg of free base per mL 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid-glycoprotein.
Lidocaine crosses the blood-brain and placental barriers presumably by passive diffusion.
Lidocaine is metabolized rapidly by the liver, the metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to but less potent than those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline.
The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.
Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 μg free base per mL. In the rhesus monkey arterial blood levels of 18-21 μg/mL have been shown to be threshold for convulsive activity.

## INDICATIONS AND USAGE

Lidocaine HCl Injection, USP with preservatives is indicated for production of local or regional anesthesia, by infiltration techniques such as percutaneous injection and by peripheral nerve block techniques such as brachial plexus and intercostal, when the accepted procedures for these techniques as described in standard textbooks are observed.

## CONTRAINDICATIONS

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.

**WARNINGS**

LIDOCAINE HYDROCHLORIDE SOLUTION FOR INFILTRATION AND NERVE BLOCK SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also **ADVERSE REACTIONS** and **PRECAUTIONS**).

DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/ OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

Local anesthetic solutions containing antimicrobial preservatives (e.g. methylparaben) should not be used for epidural or spinal anesthesia because the safety of these agents has not been established with regard to intrathecal injection, either intentional or accidental.

**PRECAUTIONS**

GENERAL: The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various regional anesthetic procedures.

Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use. (See **WARNINGS** and **ADVERSE REACTIONS**). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Syringe aspirations should also be performed before and during each supplemental injection when using indwelling catheter techniques.

When clinical conditions permit, consideration should be given to employing local anesthetic solutions that contain epinephrine for a test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Lidocaine should also be used with caution in patients with severe shock or heart block.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully circumscribed quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply. Patients with peripheral vascular disease and those with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result. Preparations containing a vasoconstrictor should be used with caution in patients during or following the administration of potent general anesthetic agents since cardiac arrhythmias may occur under such conditions.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type anesthetics are metabolized by the liver, Lidocaine Hydrochloride should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations. Lidocaine Hydrochloride should be used with caution in patients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Many drugs used during the conduction of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for the management of malignant hyperthermia should be available.

Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Proper tourniquet technique, as described in publications and standard textbooks, is essential in the performance of intravenous regional anesthesia. Solutions containing epinephrine or other vasoconstrictors should not be used for this technique.

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. USE IN THE HEAD AND NECK AREA: Small doses of local anesthetics injected into the head and neck area including retrobulbar, dental and stellate ganglion blocks may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion,

convulsions, respiratory depression and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injections of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (See **DOSAGE AND ADMINISTRATION**).

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary careful patient monitoring is essential.

Concurrent administration of vasopressor drugs (for the treatment of hypotension related to obstetric blocks) and ergot-type or oxytoxic drugs may cause severe persistent hypertension or cerebrovascular accidents.

DRUG LABORATORY TEST INTERACTIONS: The intramuscular injection of lidocaine may result in an increase in creatine phosphokinase levels. Thus, the use of this enzyme determination without isoenzyme separation as a diagnostic test for the presence of acute myocardial infarction may be compromised by the intramuscular injection of lidocaine.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

PREGNANCY: *TERATOGENIC EFFECTS, PREGNANCY CATEGORY B*: Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

LABOR AND DELIVERY: Local anesthetics rapidly cross the placenta and, when used for paracervical or pudendal anesthesia, can cause varying degrees of maternal, fetal and neonatal toxicity (See **CLINICAL PHARMACOLOGY — Pharmacokinetics**). The potential for toxicity depends upon the procedure performed, the type and amount of drug used and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

Epidural, spinal, paracervical or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. In one study paracervical block anesthesia was associated with a decrease in the mean duration of first stage labor and facilitation of cervical dilation. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. The long term significance of these observations is unknown. Fetal bradycardia may occur in 20 to 30 percent of patients receiving paracervical nerve block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. Fetal heart rate should always be monitored during paracervical anesthesia. The physician should weigh the possible advantages against risks when considering paracervical block in prematurity, toxemia of pregnancy, and fetal distress. Careful adherence to recommended dosage is of the utmost importance in obstetrical paracervical block. Failure to achieve adequate analgesia with recommended doses should arouse suspicion of intravascular or fetal intracranial injection. Cases compatible with unintended fetal intracranial injection of local anesthetic solution have been reported following intended paracervical or pudendal block or both. Babies so affected present with unexplained neonatal depression at birth, which correlates with high local anesthetic serum levels, and often manifest seizures within six hours. Prompt use of supportive measures combined with forced urinary excretion of the local anesthetic has been used successfully to manage this complication.

Case reports of maternal convulsions and cardiovascular collapse following use of some local anesthetics for paracervical block in early pregnancy (as anesthesia for elective abortion) suggest that systemic absorption under these circumstances may be rapid. The recommended maximum dose of each drug should not be exceeded. Injection should be made slowly and with frequent aspiration. Allow a 5 minute interval between sides.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when lidocaine is administered to a nursing woman.

PEDIATRIC USE: Dosages in children should be reduced commensurate with age, body weight and physical condition. See **DOSAGE AND ADMINISTRATION**.

**ADVERSE REACTIONS**

SYSTEMIC: Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported.

CENTRAL NERVOUS SYSTEM: CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

CARDIOVASCULAR SYSTEM: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

ALLERGIC: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents or to the methylparaben used as a preservative in multiple dose vials. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

NEUROLOGIC: The incidences of adverse reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. In a prospective review of 10,440 patients who received lidocaine for spinal anesthesia, the incidences of adverse reactions were reported to be about 3 percent each for positional headaches, hypotension and backache, 2 percent for shivering, and less than 1 percent each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the local anesthetic.

There have been reported cases of permanent injury to extraocular muscles requiring surgical repair following retrobulbar administration.

## OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution (see **ADVERSE REACTIONS**, **WARNINGS** and **PRECAUTIONS**).

MANAGEMENT OF LOCAL ANESTHETIC EMERGENCIES: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of convulsions, as well as underventilation or apnea due to unintended subarachnoid injection of drug solution, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).

If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

The oral $LD_{50}$ of lidocaine HCI in non-fasted female rats is 459 (346-773) mg/kg (as the salt) and 214 (159-324) mg/kg (as the salt) in fasted female rats.

## DOSAGE AND ADMINISTRATION

Table 1 (Recommended Dosages) summarizes the recommended volumes and concentrations of Lidocaine HCI Injection, USP for various types of anesthetic procedures. The dosages suggested in this table are for normal healthy adults and refer to the use of epinephrine-free solutions. When larger volumes are required only solutions containing epinephrine should be used except in those cases where vasopressor drugs may be contraindicated.

These recommended doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes and concentrations to be used depend on a number of factors such as type and extent of surgical procedure, depth of anesthesia, and degree of muscular relaxation required, duration of anesthesia required, and the physical condition of the patient. In all cases the lowest concentration and smallest dose that will produce the desired result should be given. Dosages should be reduced for children and for elderly and debilitated patients and patients with cardiac and/or liver disease.

The onset of anesthesia, the duration of anesthesia, and the degree of muscular relaxation are proportional to the volume and concentration (i.e. total dose) of local anesthetic used. Thus an increase in volume and concentration of Lidocaine HCI Injection, USP will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. Although the incidence of side effects with lidocaine is quite low, caution should be exercised when employing large volumes and concentrations since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

MAXIMUM RECOMMENDED DOSAGES: **NOTE: The products accompanying this insert do not contain epinephrine.**

ADULTS: For normal healthy adults, the individual maximum recommended dose of Lidocaine HCI with epinephrine should not exceed 7 mg/kg (3.2 mg/lb) of body weight, and, in general, it is recommended that the maximum total dose not exceed 500 mg. When used without epinephrine the maximum individual dose should not exceed 4.5 mg/kg (2 mg/lb) of body weight, and, in general, it is recommended that the maximum total dose does not exceed 300 mg. The maximum recommended dose per 90 minute period of lidocaine hydrochloride for paracervical block in obstetrical and non-obstetrical patients is 200 mg total. One half of the total dose is usually administered to each side. Inject slowly five minutes between sides (See also discussion of paracervical block in **PRECAUTIONS**).

CHILDREN: It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. For children over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child's age and weight. For example a child of 5 years weighing 50 lbs, the dose of lidocaine HCI should not exceed 75-100 mg (1.5-2 mg/lb). The use of even more dilute solutions (i.e., 0.25-0.5%) and total dosages not to exceed 3 mg/kg (1.4 mg/lb) are recommended for induction of intravenous regional anesthesia in children.

In order to guard against systemic toxicity, the lowest effective concentration and lowest effective dose should be used at all times. In some cases it will be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used.

TABLE 1 Recommended Dosages

| PROCEDURE | Lidocaine Hydrochloride Solution (without epinephrine) | | |
|---|---|---|---|
| | Conc (%) | Vol (mL) | Total Dose (mg) |
| Infiltration<br>Percutaneous | 0.5 or 1.0 | 1-60 | 5-300 |
| Peripheral Nerve Blocks e.g. | 1.5 | 15-20 | 225-300 |
| Brachial | 2.0 | 1-5 | 20-100 |
| Dental | 1.0 | 3 | 30 |
| Intercostal | 1.0 | 3-5 | 30-50 |
| Paravertebral<br>Pudendal (each side) | 1.0 | 10 | 100 |
| Paracervical<br>Obstetrical analgesia (each side) | 1.0 | 10 | 100 |
| Sympathetic Nerve Blocks e.g.<br>Cervical (stellate ganglion) | 1.0 | 5 | 50 |
| Lumbar | 1.0 | 5-10 | 50-100 |

THE ABOVE SUGGESTED CONCENTRATIONS AND VOLUMES SERVE ONLY AS A GUIDE. OTHER VOLUMES AND CONCENTRATIONS MAY BE USED PROVIDED THE TOTAL MAXIMUM RECOMMENDED DOSE IS NOT EXCEEDED.

STERILIZATION, STORAGE AND TECHNICAL PROCEDURES: Disinfecting agents containing heavy metals which cause release of respective ions (mercury, zinc, copper etc.) should not be used for skin or mucous membrane disinfection as they have been related to incidents of swelling and edema. When disinfection of multi-dose vials is desired either isopropyl alcohol (91%) or 70% ethyl alcohol is recommended. Many commercially available brands of rubbing alcohol, as well as solutions of ethyl alcohol not of USP grade, contain denaturants which are injurious to rubber and therefore are not to be used.

FOR INFILTRATION AND NERVE BLOCK. NOT FOR EPIDURAL OR CAUDAL USE.

**HOW SUPPLIED**

Lidocaine Hydrochloride Injection, USP.

NDC 0517-0625-25 1% 50 mL Multiple Dose Vials*
packed in boxes of 25

NDC 0517-0626-25 2% 50 mL Multiple Dose Vials*
packed in boxes of 25

*Multiple Dose Vials are preserved with Methylparaben.

Store at controlled room temperature 15°-30°C (59°-86°F) (See USP).

IN0625
Rev. 10/03
MG #14438

AMERICAN
REGENT, INC.
SHIRLEY, NY 11967